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Microstructural brain reorganization in chronic gastrointestinal disorders

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Irritable bowel syndrome (IBS), which is defined by chronic abdominal pain associated with diarrhea and/or constipation, bloating, and urgency, is one of the most common functional gastrointestinal disorders in the United States. The pathophysiology of IBS remains poorly understood; however, it is significant that many IBS patients also exhibit a wide variety of somatic symptoms, including back pain, migraine headaches, heartburn, dyspareunia, and muscle pain in body regions somatotopically distinct from the gut. Indeed, these IBS patients with hypersensitivity also exhibit visceral and somatic hypersensitivity, which suggests that abnormalities in peripheral and/or central pain processing contribute [12]. Further support for altered central nervous system (CNS) processing in IBS patients stems from several neuroimaging studies that have clearly demonstrated altered brain activation compared to controls in response to noxious stimuli [7,9,11]. Ongoing sensitization of both visceral and somatic afferents may lead to altered input to the central neuroaxis, which ultimately induces persistent CNS changes, as occurs in similar chronic pain syndromes, such as temporomandibular disorder [8]. Thus, given the strong evidence for the presence of altered central pain processing in IBS patients, could long-term microstructural reorganization of the brain also contribute to the chronic pain and gastrointestinal symptoms experienced by IBS patients?

The study by Ellingson et al. in the current issue of *PAIN*® examines this question [4]. The investigators hypothesized that IBS patients with chronic visceral pain have long-term microstructural changes within the brain, particularly in regions associated with integration of sensory information and corticothalamic modulation. Many studies have shown that the basal ganglia is an important contributor to the integration of multiple sensory and nonsensory information leading to interpretation and modulation of both acute and chronic pain in persistent pain disorders, including IBS [10]. Based on these observations, the authors further proposed that IBS patients have microstructural alterations within regions of the homeostatic afferent network and the basal ganglia.

The current elegant study utilized diffusion tensor imaging, a magnetic resonance imaging technique that can detect subvoxel microstructural information within tissues. Diffusion tensor imaging measures both the magnitude and directionality of water self-diffusion [1]. This technique includes measures of fractional anisotropy (a scalar measure of relative

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diffusion anisotropy) and average apparent diffusion coefficient (mean diffusivity), which have both been used as surrogate measures of human brain microstructural integrity. Of interest, recent preliminary studies using diffusion tensor imaging in chronic pain patients, including IBS patients, have demonstrated microstructural changes within sensory processing regions [2,3,5,6]. In contrast to these earlier studies, Ellingson et al. performed voxel-wise diffusion tensor imaging measurements within deep gray matter structures and in white matter tracts, in a large cohort of well phenotyped IBS patients (n = 33) and healthy controls (n = 93) [4]. In addition, the authors used probabilistic diffusion tensor imaging tractography to examine differences in the number of fiber tract connections between areas of the brain involved in pain processing in IBS patients and controls.

The results from the current study demonstrate that microstructural reorganization of chronic pain pathways does occur in IBS patients, which is consistent with previous studies in other persistent pain conditions, including chronic pain in IBS patients [7,9,11]. A significant correlation was present between symptom severity and connectivity between the thalamus and somatosensory cortex, as well as between the thalamus and insula. Interestingly, the most pronounced microstructural findings that differentiated IBS patients from healthy controls were seen in the basal ganglia and thalamus. Since the basal ganglia acts as a multisensory integration site and has multiple connections to the thalamus and cortical sites, it may serve to modulate pain behavior and learning in IBS patients. Indeed, the abnormalities seen between these corticobasal ganglion-thalamic-cortical circuits may serve to modulate complex interactions between behavior, emotion, and pain in IBS patients and other chronic pain conditions such as interstitial cystitis, vulvodynia, and fibromyalgia. Could reductions in axon and dendrite density in the corticobasal ganglia-thalamic-cortical loops that modulate pain be a common underlying factor that coalesces pain behavior in chronic visceral and somatic pain disorders such as IBS and fibromyalgia? The authors suggest that in IBS patients, impairment of corticobasal ganglia-thalamic cortical loops may be due to: 1) chronic prefrontal cortex activation in response to anticipation of visceral pain/discomfort; 2) modulation of chronic sensory input; 3) the presence of persistent and increased viscerosensory input due to visceral hypersensitivity that arises secondary to sensitized primary visceral afferent pathways. Chronic afferent barrage from the gut leading to CNS molecular and gene changes that create a chronic feedback loop via a homeostatic cross-talking network [12] may also contribute to microstructural changes in IBS patients.

The results of the Ellingson et al. study [4] have significant implications and provide challenges for future studies that evaluate microstructural reorganization of the brain (Fig. 12 in [4]) in IBS patients. Although microstructural changes that correlated with symptom severity were noted in IBS patients compared to controls, the specific cell types involved could not be delineated with diffusion tensor imaging. A further challenge going forward is that patients with chronic pain syndromes often have significant underlying anxiety and depression, with corresponding white matter and subcortical gray matter changes. In fact, the current study excluded patients with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th Revision diagnosis of psychiatric disease. Clearly, future studies should examine the differential contribution of persistent pain syndromes vs psychological disorders in microstructural brain changes. Longer-term longitudinal studies of IBS patients

should also be performed so as to determine the time course over which CNS changes occur and fluctuate in response to therapeutic interventions.

References

1. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994; 66:259–67. [PubMed: 8130344]
2. Buckalew N, Haut MW, Aizenstein H, Morrow L, Perera S, Kuwabara H, Weiner DK. Differences in brain structure and function in older adults with self-reported disabling and nondisabling chronic low back pain. Pain Med. 2010; 11:1183–97. [PubMed: 20609128]
3. Chen JY, Blankstein U, Diamant NE, Davis KD. White matter abnormalities in irritable bowel syndrome and relation to individual factors. Brain Res. 2011; 1392:121–31. [PubMed: 21466788]
4. Ellingson BM, Mayer E, Harris RJ, Ashe-McNally C, Naliboff BD, Labus JS, Tillisch K. Diffusion tensor imaging detects microstructural reorganization in the brain associated with chronic irritable bowel syndrome. PAIN®. 2013; 154:1528–41. [PubMed: 23721972]
5. Farmer MA, Chanda ML, Parks EL, Baliki MN, Apkarian AV, Schaeffer AJ. Brain functional and anatomic changes in chronic prostatitis/chronic pelvic pain. J Urol. 2011; 186:117–24. [PubMed: 21571326]
6. Frokjaer JB, Olesen SS, Gram M, Yavarian Y, Bouwense SA, Wilder-Smith OH, Drews AM. Altered brain microstructure assessed by diffusion tensor imaging in patients with chronic pancreatitis. Gut. 2011; 60:1554–62. [PubMed: 21610272]
7. Mayer EA, Tillisch K. The brain-gut axis in abdominal pain syndromes. Annu Rev Med. 2011; 62:381–96. [PubMed: 21090962]
8. Moayedi M, Weissman-Fogel I, Salomons TV, Crawley AP, Goldberg MB, Freeman BV, Tenebaum HC, Davis KD. White matter brain and trigeminal nerve abnormalities in temporomandibular disorder. PAIN®. 2012; 153:1467–77. [PubMed: 22647428]
9. Price DD, Craggs JG, Zhou Q, Verne GN, Perlstein WM, Robinson ME. Widespread hyperalgesia in irritable bowel syndrome is dynamically maintained by tonic visceral impulse input and placebo/nocebo factors: evidence from human psychophysics, animal models, and neuroimaging. Neuroimage. 2009; 47:995–1001. [PubMed: 19375508]
10. Tillisch K, Mayer EA, Labus JS. Quantitative meta-analysis identifies brain regions activated during rectal distension in irritable bowel syndrome. Gastroenterology. 2011; 140:91–100. [PubMed: 20696168]
11. Verne GN, Himes NC, Robinson ME, Gopinath KS, Briggs RW, Crosson B, Price DD. Central representation of visceral and cutaneous hypersensitivity in the irritable bowel syndrome. PAIN®. 2003; 103:99–110. [PubMed: 12749964]
12. Zhou Q, Fillingim RB, Riley JL, Malarkey WB, Verne GN. Central and peripheral hypersensitivity in the irritable bowel syndrome. PAIN®. 2010; 148:454–61. [PubMed: 20074857]